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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,183	11/14/2003	Dean L. Engelhardt	Enz-52(D2)(C)(D1)	5179

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,183	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112-148* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *112-148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3132008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 4/21/2008.

2. Currently Claims 112-148 are pending.

3. The following rejections for Claims 112-148 are newly applied. Specifically the double patenting rejection has been newly applied. Response to arguments follows.

4. This action is Non-FINAL.

Priority

5. It is noted that priority has been granted in the petition decision mailed 1/23/2008. As such the filing date is 01/13/1994.

Withdrawn Objections and Rejections

6. The objection to the abstract made in the nonfinal (6/02/2006) in section 4 is moot based upon amendments to the specification.

7. The objection to the specification made in the non-final (6/02/2006) in section 5 is moot based upon amendments to the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. It is noted that the following 35 USC 103(a) rejections are newly applied.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 112-121, 123-130, 133-143, 145-146, 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al. (US Patent 5,169,766 December 8, 1992) in view of Scheele (US Patent 5162209 November 10, 1992).

With regard to Claim 112 and 123, Schuster et al. teaches a method of amplifying a nucleic acid molecule. Schuster et al. teaches providing a DNA target (Figure 3 ssDNA analyte). Schuster et al. teaches mixing the target with nucleoside triphosphates (nucleic acid precursors) (Column 7, lines 60-65). Schuster et al. teaches

the proto-primer used can be a RNA sequence (Column 11, lines 47-51). Schuster et al. teaches the use of RNase H to remove RNA from the cDNA (Column 8, lines 7-10).

Schuster et al. teaches making RNA: DNA hybrid (Column 9, lines 32-33). Schuster et al. teaches an mRNA promoter (primer) which is used to extend and make ssRNA (Figure 3).

Schuster et al. teaches another primer (DNA) is annealed to the ssRNA and cDNA is copied (Figure 3).

Schuster et al. teaches the ssRNA (which is the extended promoter-primer) is destroyed by RNase H (Figure 3). Schuster et al. teaches that this method cyclical and therefore can produce multiple copies (Column 4 lies 50-54). Therefore after the RNA is destroyed another primer can anneal to the nucleic acid sample.

With regard to Claim 133, Schuster et al. teaches a method of amplification in which the desired nucleic acid molecules can be RNA (Column 9, lines 52-53). Schuster et al. teaches a method of amplification in which a starting ssRNA analyte is primed in conditions for replication, a double stranded DNA template is produced, and RNase H is used to remove the RNA primers segment to allow the next priming event to occur (Figure 2).

With regard to Claims 113, 124, and 134, Schuster et al. teaches the use of primers which are chemically modified by blocking the 3' terminus using a 3' terminal nucleotide lacking a 3' hydroxyl group (modified nucleotides) (Column 11 lines 60-64).

With regard to Claims 114-115, 125-126, 135-136, and 142, Schuster et al. teaches a promoter primer which has at least 1 noncomplementary nucleotides (Figure 1 2nd step).

With regard to Claims 116, and 137, Schuster et al. teaches that the modified proto-primer can be RNA; therefore it is inherent that an RNA strand would be composed of deoxyribonucleotides (Column 11, lines 47-60).

With regard to Claims 117-119, 127-130, and 138-140, Schuster et al. teaches DNA polymerase (nucleic acid catalyst) include Taq polymerase, Klenow polymerase, E. coli polymerase, and T7 DNA polymerase (Column 7, lines 14-20).

With regard to Claims 120 and 141, Schuster et al. teaches mixing the target with nucleoside triphosphates (nucleic acid precursors) (Figure 1 Column 7, lines 60-65).

With regard to Claims 121, Schuster et al. teaches the use of primers which are chemically modified by blocking the 3' terminus using a 3' terminal nucleotide lacking a 3' hydroxyl group (Column 11 lines 60-64).

With regard to Claim 143 and 146, Schuster et al. teaches a method of amplifying a nucleic acid molecule. Schuster et al. teaches providing a DNA target (Figure 3 ssDNA analyte). Schuster et al. teaches mixing the target with nucleoside triphosphates (nucleic acid precursors) (Column 7, lines 60-65). Schuster et al. teaches the proto-primer used can be a RNA sequence (Column 11, lines 47-51). Schuster et al. teaches the addition of a polymerase (Column 7, lines 14-20). Schuster et al. teaches the use of RNase H to remove RNA from the cDNA (Column 8, lines 7-10, Figure 3).

Schuster et al. teaches producing a copy of a specific nucleic acid (Figure 3) and removing ribonucleotides using RNase H(Figure 3). Schuster et al. teaches an mRNA promoter (primer) which is used to extend and make ssRNA (Figure 3). Schuster et al. teaches the ssRNA (which is the extended promoter-primer) is destroyed by RNase H (Figure 3). Schuster et al. teaches that this method cyclical and therefore can produce multiple copies (Column 4 lies 50-54). Therefore after the RNA is destroyed another primer can anneal to the nucleic acid sample.

With regard to Claims 145 and 148, Schuster et al. teaches a promoter primer which has at least 1 noncomplementary nucleotides (Figure 1 2nd step).

However, though Schuster et al. teaches that the primer can be RNA (Column 11, lines 47-51), Schuster et al. does not teach that the RNAse H is used to digest the substrate to remove the RNA segment of the primer.

Scheele et al. teaches a method for preparing a dsDNA from a ssDNA (abstract). Scheele et al. teaches a method of providing a first DNA strand, contacting with a primer, synthesizing in the presence of the primer that contains RNA and producing a copy of the DNA template (abstract). Scheele et al. teaches that RNA primers can be digested using RNAse H (Column 6 lines 65-68).

Therefore it would be prima facie obvious to one of ordinary skill in the art to digest the RNA primer of Schuster et al. with the RNAse H which is already in the solution because Scheele et al. teaches that RNAse H digest RNA primers on a DNA/RNA hybrid strand. The ordinary artisan would be motivated to digest all RNA

which is in the system in the double stranded form (e.g. DNA/RNA) in order to produce multiple copies of the nucleic acids of interest.

Response to Arguments

The reply traverses the rejection. A summary of the arguments made in the reply is presented below with response to arguments following.

(A) The reply asserts that Schuster does not teach step d of Claim 112 (p. 23 2nd paragraph). The reply asserts that in the instant invention the substrate is an extended primer bound to the nucleic acid of interest and thus when the RNA segment of the primer is removed a binding site is regenerated on the nucleic acid of interest (p. 23 2nd paragraph). The reply asserts that in contrast Schuster RNA copies are made off the original template and these copies do not comprise the primers themselves and as such may show removal of primer-derived copies but there is no removal of RNA segments from the primers as such primer binding events only take place on resultant copies and the primer is not removed from the original template (p. 23 2nd paragraph).

The reply asserts that RNaseH requires the presence of an RNA/DNA temple and will not act of a single stranded RNA sequence (p. 23 last paragraph and p. 24 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is acknowledged that RNaseH requires the presence of an RNA/DNA template and will not act on a single stranded RNA sequence. However, Schuster et al. teaches

that the protoprimer can be composed of RNA (Column 11, lines 47-51). Schuster et al. teaches the addition of RNase H. Scheele et al. teaches that RNA primers can be digested using RNAse H (Column 6 lines 65-68). Therefore in the case of the proto-primer comprising RNA, the RNA would be digested and the primer binding site would be open for further replication. Further the limitation that the same primer binding events occur with the original template is not a limitation of the claims. The claims are drawn to "allowing another primer binding event to occur with said nucleic acid of interest". Therefore the "another primer binding event" could be a primer binding event in another region of the template. Said nucleic acid of interest could refer to the original template, but since the produced nucleic acid is identical to the original template could refer to the produced nucleic acid.

(B) The reply asserts with regard to Claims 133-142, that Schuster et al. uses an RNA copy to make a cDNA copy (p. 24 last paragraph). The reply asserts that RNase H is used to produce single stranded cDNA molecules, therefore the method to make double stranded molecule which is DNA/DNA is not followed by RNase H as required by step e of Claim 133. The reply asserts Schuster et la. never removes an RNA segment with RNase H from a double stranded copy (step d) made after a DNA copy is made from a DNA copy (step e) (p. 24 last paragraph and p. 25 1st paragraph). The reply asserts that there is never discussion or suggestion of removal of RNA from primers only digestion of RNA copies that have been generated from primer sequences (p. 25 1st paragraph).

This argument has been fully reviewed but has not been found persuasive.

With regard to Claim 133, Schuster et al. teaches a method of amplification in which the desired nucleic acid molecules can be RNA (Column 9, lines 52-53). Schuster et al. teaches a method of amplification in which a starting ssRNA analyte is primed in conditions for replication, a double stranded DNA template is produced, and RNase H is used to remove the RNA primers segment to allow the next priming event to occur (Figure 2). As discussed above, Schuster et al. teaches that the protoprimer can be composed of RNA (Column 11, lines 47-51). Schuster et al. teaches the addition of RNase H. Scheele et al. teaches that RNA primers can be digested using RNAse H (Column 6 lines 65-68). Therefore in the case of the proto-primer comprising RNA, the RNA would be digested and the primer binding site would be open for further replication. Therefore the RNA segment of the primers would be digested with RNase H and as such only the sense strange of the original RNA analyte will be in the system (Figure 4).

(C) The reply asserts that a chimeric primer is not described in Schuster et al. as disclosed in the previous office action (p. 25 4th paragraph).

This argument has been fully considered and is found persuasive.

It is acknowledged that Schuster et al. does not teach copolymer primers.

However, as discussed below, it would be obvious for the ordinary artisan to modify the teachings of Scheele et al. and Schuster al. to use copolymer primers.

11. Claim 122, 131-132, 144 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster et al. (US Patent 5,169,766 December 8, 1992) in view of Scheele (US Patent 5162209 November 10, 1992) as applied to claims 112-121, 123-130, 133-143, 145-146, 148 and further in view of Kacian et al. (US Patent 5554516 September 10, 1996).

Schuster et al. and Scheele et al. teach a method of in vitro transcription. Schuster et al. teaches the use of primers which are chemically modified by blocking the 3' terminus using a 3' terminal nucleotide lacking a 3' hydroxyl group (Column 11 lines 60-64).

Schuster et al. and Scheele et al., however, do not teach primers modified by heteroatoms comprised of nitrogen or sulfur and chemically modified primers comprised of nucleoside triphosphates or the use of copolymer primers.

Kacian et al. teaches a method of amplifying a target nucleic acid sequence (Abstract). Kacian et al. teaches a method of incubating a promoter-primer and a target sequence in DNA priming and nucleic acid synthesizing conditions (ribonucleotide triphosphates and deoxyribonucleotide triphosphates) (nucleic acid precursors) for a period of time to many multiple copies of the target sequence (Column 10 lines 23-33).

With regard to Claims 122, 131, and 132, Kacian et al. teaches that the 3' end of the promoter-primer may be modified (Column 7 line 6). Kacian et al. teaches that one modification can be the addition of a phosphorothioate (sulphur heteroatom) (Column 10 lines 22-33).

With regard to Claims 144 and 147, Kacian et al. teaches the promoter-primer may be altered with ribonucleotides (Column 9, line 15). Therefore the promoter-primer can be RNA: DNA mixture. Kacian et al. teaches the promoter-primer can have both RNA and a DNA region (Column 9, line 15).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Schuster et al. and Scheele et al. to use the modified ends and the copolymer primers as taught by Kacian et al. The ordinary artisan would have been motivated to modify the method of Schuster et al. and Scheele et al. to use the modified ends and the copolymer primers as taught by Kacian et al., because Kacian et al. teaches that primers can be blocked to inhibit extension from the 3' end of the primer such that only the nucleic acid sequence extending from the primer form the 3' end is amplified (column 6 lines 55-67 and column 7 lines 1-20). The ordinary artisan would be motivated to use copolymers as taught by Kacian et al. because Kacian et al. teaches that the promoter primer can include the addition of ribonucleotides or deoxynucleotides residues to effectively block the 3' end (Column 9 lines 10-25).

Response to arguments

The reply traverses the rejection. A summary of the arguments made in the reply is presented below with response to arguments following.

The reply asserts that neither Kacian et al. nor Schuster et al. teach step d of the claimed invention (p. 31 2nd paragraph).

This argument has been fully reviewed but has not been found persuasive. Schuster et al. teaches a method of amplifying a nucleic acid molecule. Schuster et al. teaches providing a DNA target (Figure 3 ssDNA analyte). Schuster et al. teaches mixing the target with nucleoside triphosphates (nucleic acid precursors) (Column 7, lines 60-65). Schuster et al. teaches the proto-primer used can be a RNA sequence (Column 11, lines 47-51). Schuster et al. teaches the addition of a polymerase (Column 7, lines 14-20). Schuster et al. teaches the use of RNase H to remove RNA from the cDNA (Column 8, lines 7-10, Figure 3). Scheele et al. teaches that RNA primers can be digested using RNAse H (Column 6 lines 65-68). Therefore the combination of Schuster et al. and Scheele et al. teach all the limitation of the independent claims. As presented above the ordinary artisan would be motivated to modify the method of Schuster et al. and Scheele et al. with Kaician et al. in order to produce copolymer primers and primers which are chemically modified.

Double Patenting

12. The following double patenting rejection has been newly applied.

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 91-101 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 91-99 of copending Application No. 10/718391. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 91-101 of the instant application describes the same method steps as Claim 91-99 of application 10/718391. Both applications are drawn to a method of producing copies of a specific nucleic acid by providing a nucleic acid sample, contacting it with unmodified nucleic acid precursors and modified RNA primers. Both applications use a catalyst. Both applications modify primers using hereoatoms comprising nitrogen or sulfur. Both applications claims are drawn to primers, which comprise about 1 to about 200 noncomplementary nucleotide or nucleotide analogs. The primers of the instant application are encompassed by the genus of generic primers claimed by 10/718391. The specification of 10/718391 defines a primer as DNA, RNA, or DNA:RNA, therefore the claims of 10/718391 are drawn to a method using a genus of primers which include the RNA primer and the DNA:RNA primer of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claims are allowable over the cited prior art.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Katherine Salmon/
Examiner, Art Unit 1634

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1634